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Efficacy and tolerability of add-on Lacosamide treatment in adults with Lennox–Gastaut syndrome: An observational study

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ABSTRACT

Purpose: To evaluate the efficacy, safety, and tolerability of lacosamide in adults with LGS in the clinical setting.
Method: The present report is a retrospective, open-label treatment study carried out from June 2013 to December 2014 at the National Institute of Colombia. Lacosamide was introduced as add-on therapy. All caregivers were instructed to initiate lacosamide at low doses (25–50 mg) and gradually increasing it every 2 weeks. The efficacy was evaluated based on the reduction in the rate of each countable type of seizure. We also evaluated the retention rate for lacosamide as the number of days with lacosamide during follow-up. The tolerability was evaluated base on account the adverse events.
Results: We found that lacosamide only improves the seizure rate in three out of 19 patients with LGS, in two of them by more than 50%. The highest seizure reduction rate was observed in the focal and tonic-clonic seizures. The most commonly reported adverse events were worsening of seizures, aggressiveness and irritability. Nine patients (47.4%) showed worsening of their behavior during the treatment with lacosamide.
Conclusion: Lacosamide can exacerbate both, the tonic and astatic seizures, and the encephalopathy associated with this epileptic syndrome. However, it is interesting to consider the likelihood of suppression of generalized tonic-clonic and focal seizures. That is why; lacosamide could be an option after carefully balancing risks and benefits in each individual case.

1. Introduction

Unlike to Lennox–Gastaut syndrome (LGS) in childhood, which has been extensity studied [1], less is known about the electroclinical features and treatment of LGS in adult life. Such syndrome is characterized by multiple, drug-resistant seizure types and progressive mental deterioration after epilepsy onset [2]. Nevertheless, some atypical features have been described in adult patients with this syndrome [2,3]. Because of that, the choice of the antiepileptic medication could be different.

Lacosamide (LAC) is one of the latest anti-epileptic drugs (AEDs) available on the market [4]. Potential mechanisms of action include the enhancement of slow inactivation of voltage-gated sodium channels, which leads to an increased proportion of sodium channels unavailable for depolarization [4]. LAC has a favorable profile as it is completely absorbed after oral administration exhibiting 15% of protein binding [4,5]. The drug has not been shown to induce or inhibit CYP enzymes in preclinical/clinical studies examining specific CYP substrates [4]. Although double blind placebo-controlled clinical trials demonstrated the efficacy of LAC in adults with partial onset seizures [6–9], the efficacy and tolerability of LAC in the treatment of generalized epileptic syndromes like LGS in childhood and adult patients have yet to be clarified.

Grosso et al. reported a retrospective, multicenter study, which was conducted to evaluate the efficacy and safety of LAC in

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children affected by LGS [10]. The authors concluded that a third of the children with LGS responded to LAC as an add-on therapy, thus they suggested that LAC might be effective and represent of a possible therapeutic option in children affected by LGS [10]. This study was criticized because of some methodological issues; thus, some authors suggested to use LAC cautiously in children with LGS. To review the principal criticism/comments to this study, we recommend to read two letters to the editor that were published by Andrade-Machado et al. and Italiano et al. last year in Acta Neurological Scandinavica [11,12].

Studies of the use of LAC in adult patients with LGS are scarce and limited to case reports. Cuzzola et al. published in 2010 three adult cases with LGS who developed seizure worsening after introducing LAC as an add-on therapy [13]. Andrade-Machado et al. in 2012, reported a tonic status epilepticus induced by LAC in an adult male with LGS; in that report the authors also showed a worsening in one of the characteristic electrographic patterns of this epileptic syndrome, generalized paroxysmal fast activity (GPFA) [14].

Considering the limitations of the above-mentioned case reports and the study carried out by Grosso et al. in children, we conducted a retrospectively analysis of 19 adult patients with LGS in which LAC was used as an add-on therapy to improve seizure control as a desperate measure after multiple antiepileptic drugs, corpus callosotomy surgery or vagal nerve stimulation (VNS) failures. We aimed to observe the efficacy, safety, and tolerability of LAC in adults with LGS in the clinical setting.

2. Patients and methods

This is a retrospective, open-label treatment study carried out from June 2013 to December 2014 at the National Institute of Colombia. All patients were recruited from our outpatient facilities (five in the case of adults with epilepsy). In our institution all the patients who require a video-EEG recording are evaluated in our neurophysiology unit. A total of 35 adults with LGS have been diagnosed in our institution since 2012. Nineteen of them have been treated with LAC as add on therapy. In those patients, LAC was introduced as an add-on therapy because all previous therapies have failed but not for research purposes. The institutional ethical committee approved the present study. Written informed consent before LAC was added to their treatment was not requested.

2.1. Inclusion criteria:

(i) Age above 16 years; (ii) LGS refractory to at least three previous antiepileptic drugs (AEDs), alone or in combination; (iii) exhibiting at least four seizures per month during the 3 months before LAC was introduced; (iv) use of at least one other AED; (v) to have a 24 h video-electroencephalographic monitoring in the 3 months before the introduction of LAC.

All seizures were classified according to the International League Against Epilepsy Revised Classification of Seizures, while diagnostic criteria for LGS were based on the following criteria: (i) polymorphous seizures including tonic–axial, and at least one of the following seizure types should be present: astatic, atonic or atypical absences. The presence of myoclonic, GTCS or partial seizures were not a cause for exclusion; (ii) EEG abnormal EEG background activity, slow spike-waves <3 Hz and, often, multifocal abnormalities and bursts of 10 Hz fast rhythms during sleep; (iii) in general, mental retardation.

The diagnosis of LGS in all patients included in the study was corroborated with a 24 h video-electrographic monitoring TV recording. All traces were evaluated by two neurologist (RAM and JFAR) with special expertise in the diagnosed of electroclinical epileptic syndromes.

All patients underwent brain 1.5 T magnetic resonance imaging (MRI), biochemical analyses, chromosomal investigations and screening for metabolic diseases. Also all patients had a formal neuropsychological evaluation prior to the use of lacosamide.

2.2. Information about how the study data was gathered:

The study began in June 2013 and finished in December 2014 (18 months of follow-up). In our institution each patient visits our outpatient facility every 3 months. To facilitate the understanding of the present study, we considered the entry to the study when a patient was instructed to receive LAC. All caregivers were instructed to initiate lacosamide at low doses (25–50 mg per day with gradually increasing the dose every 2 weeks until reaching 200 mg per day. The present study is retrospective and represents the daily clinical practice; the doses reported were those reported in the medical records according to the prescription made by the neurologist in the outpatient clinical setting. During treatment, general and neurological examinations were performed every 3 months in all patients. LAC serum levels were not measured because of lack of availability in our laboratories.

According to the institution protocols each caregiver has a seizure calendar to annotate the frequency, semiology and precipitants of seizures and the possible side effects of the medications. This calendar was review by the Neurologist in each visit and registered in medical records. As all patients had a calendar, the basal seizure frequency was analyzed base on the frequency per months during the 3 months before LAC was introduced.

In order to improve the care of the patients, our institution has an epilepsy program carried with a multidisciplinary group including social worker, general physicians, nurses, neurologists and epileptologists. During each visit, the family/caregivers (in cases of patients with severe disabilities) were questioned about the patient's behavior, learning and independence, needing of psychiatrics or pedagogic accompanying and previous admissions to other institutions. All information regarding the above-mentioned aspects, are then registered in the patient medical record.

Complete peripheral blood counts, urinary analysis, blood creatinine and alanine and aspartate aminotransferase levels were also monitored, and when possible, blood levels of concomitant AEDs.

Treatment was discontinued when the neurologist considered that it was not effective or in cases in which seizure aggravation was suspected. As this study has a retrospective design, concomitant drug regimen could be changed during the retrospective baseline phase. Review of the medial records showed the following changes in the concomitant AEDs: Vigabatrin was discontinued in two patients after 6 months of follow-up and Valproate in two patients after 3 months of follow-up. The remaining AEDs were not changed.

2.3. Evaluation of efficacy:

Efficacy was evaluated based on the reduction in the rate of each countable type of seizure. The percentages of patients with more than 50% and less than 50% but more than 25% reduction in seizure frequency, were also assessed, and both were defined as responder. We also evaluated the difference between seizure frequencies before and after LAC was introduced. Treatment was considered as not effective when the doses of 200–300 mg per day were reached and no seizure improvement was reported. In patients in whom LAC was not dropped out because of adverse effects or seizures aggravation, the difference between the seizure frequency before and after LAC was introduced, was calculated after 18 months of follow-up.

Due to the difficulty in determining the frequency of atypical absences and myoclonic seizures, we did not provide data on the efficacy of lacosamide for this type of seizures.

We also evaluated the retention rate for lacosamide as the number of days with LAC during the follow-up.

2.4. Evaluation of tolerability:

Efficacy was evaluated based on the reduction in the rate of each countable type of seizure. The percentages of patients with more than 50% and less than 50% but more than 25% reduction in seizure frequency, were also assessed, and both were defined as responders. We also evaluated the difference between seizure frequencies before and after LAC was introduced. Treatment was considered as not effective when the doses of 200–300 mg per day were reached and no seizure improvement was reported. In patients in whom LAC was not dropped out because of adverse effects or seizures aggravation, the difference between the seizure frequency before and after LAC was introduced, was calculated after 18 months of follow-up.

Due to the difficulty in determining the frequency of atypical absences and myoclonic seizures, we did not provide data on the efficacy of lacosamide for this type of seizures.

We also evaluated the retention rate for lacosamide as the number of days with LAC during the follow-up.

2.5. Evaluation of tolerability:

The presence of adverse events was obtained retrospectively from medical records and from the parents/caregivers, by telephone conversation carried out by the authors of this investigation at the moment of database completion. Information obtained from medical records included: 1. Vital signs, general and neurological examination. 2. Adverse events reported by the Epileptologists. 3. Laboratory values (blood and urinary tests). The data evaluated were obtained from each visit during the last 18 months. By telephone conversation each parent/caregivers was requested to respond the following question: during or after treatment with LAC, have you felt that your child has suffered or reported one of the following symptoms?: dizziness, sedation, headache, tremor, ataxia, rash, diplopia, fatigue, weight gain, depression, worsening of seizures, agitation, dysarthria, insomnia, vomiting, withdrawal because of side effects, or something else that you consider to mention. All the reported symptoms were taking into account.

Possible effects on behavior, and the possibility of inducing or aggravating typical seizures in LGS (paradoxical reaction) as it has been previously reported, was also evaluated.

Effects of LAC on behavior were evaluated following a *Likert*'s scale constructed for the purposes of the present study:

2.6. Behavior before/after LAC introduction:

Patient with total independence for daily activities (dressing, bathing and eating without assistance), without psychiatric medications and schooled = 0; patient with total independence for daily activities (dressing, bathing and eating without assistance), is on psychiatric medications to control his/her behavior and is schooled = 1; patient with total independence for daily activities (dressing, bathing and eating without assistance), is on psychiatric medications to control his/her behavior and is not schooled = 2; patient with total dependence for daily activities, is on psychiatric medications to control his/her behavior and is not schooled = 3; patient with total dependence for daily activities, is on psychiatric medications but it is not enough to control his/her behavior, is not schooled but does not require custody = 4; patient who require custody to avoid damage to him/herself, and the psychiatric medication does not control his/her behavior.

The data required for behavior scale was obtained from the medical record and telephone conversations with the parents at the moment of database completion for the study.

The Institutional Review Board and ethical committee approved this investigation.

2.7. Statistical analysis:

Data was processed with STATISTIC software version 6.0 and presented in tables and graphics. All data are presented as frequencies and percentages. For comparison of quantitatively non-continuous variables (before/after rank ordering of observations), the Wilcoxon matched pair test was used. For comparison of qualitative variables chi-square test was used. Due to the small sample analyzed, to evaluate whether the etiology influence on therapeutic response, the symptomatic and cryptogenic subgroups were compared considering whether or not there was seizure improvement or the likelihood of worsening of seizures after treatment, according to each type of seizure. For this purpose chi-square test was used. The results were considered statistically significant when p value was <0.05.

3. Results

We included 19 patients (12 males, 7 females), aged between 18 and 61 years (mean 27.1 $\pm$ 14.2), who were under LAC as an add-on therapy. Nineteen patients (100%) had tonic seizures, 18 (94.7%) had astatic and atypical absences seizures, 16 (84.2%) had atonic seizures, and 3 (15.8%) had focal seizures. Seven patients were diagnosed as cryptogenic and 12 as symptomatic LGS. All patients had mental retardation. All (19/19) had paroxysmal fast activity and generalized <3 Hz SW (100%), and focal paroxysmal discharges were documented in 12 of 19 patients (Table 1).

Mean age at the time of seizure onset was 4.6 (range: 1–15 years). Mean duration of epilepsy was 22.5 years (range: 8–59). Seizure frequency during baseline phase was the following: tonic seizures >30/day (nine patients); ≤30/day (10 patients); astatic seizures >10/day (four out of 18 patients); tonic-clonic seizures <10/day (15 out of 19 patients); focal seizures <10/day (three out of 19 patients).

Before the LAC trial, patients had been treated with 1–4 AEDs. Nine out of 19 patients (47.4%) were treated with two AEDs. The most commonly used concomitant antiepileptic comedication was levetiracetam (14 patients). Four patients had vagus nerve stimulation therapy prior to starting LAC and in seven callosotomy was performed before the introduction of LAC. LAC was administered in two equal daily doses: median of initial dose of 25 mg (range 25–50). The range of maximum doses was between 50 mg and 300 mg, with a median of 200 mg.

The clinical efficacy according to seizure type and etiology is summarized in Table 2. LAC reduced the seizure frequency by more than 50% in two (10.5%) patients responder and by less than 50% in other one patient (5.3%). In 16 (78.9%) patients an increased in tonic seizure frequency was documented, and 3 out of 19 (15.8%) reported no changes in tonic seizures during treatment. Seven of 18 patients reported an increase in astatic seizures. The frequency of tonic-clonic seizures was not increased during LAC treatment. The highest seizure reduction rate was observed in the focal and tonic-clonic seizures. We did not found a significant statistical association between the etiology (symptomatic or cryptogenic) and the reduction of frequency of atonic, tonic and tonic-clonic seizures ($p > 0.05$), number of patients with tonic status or repetitive cluster of tonic seizures ($p > 0.05$) and number of

Table 1
Clinical findings of patients.

Characteristics	Value
Age (years) mean ± SD range	27.1 ± 14.2 (18–61)
Sex M/F	12 (63.2)/7 (36.8)
Age at seizure onset (years) mean ± SD range	4.6 ± 2.7 (1–15)
Seizure types, *n* (%)	
Tonic	19 (100)
Atonic	16 (84.2)
Atypical absences	18 (94.7)
Astatic	18 (94.7)
TCS	15 (78.9)
Myoclonic seizures	5 (26.3)
Focal seizures	3 (15.8)
Etiology classification, *n* (%)	
Symptomatic	7 (36.8)
Cryptogenic	12 (63.2)
Mental retardation	19 (100)
Epilepsy duration (years) mean ± SD range	22.5 ± 14.6 (8–59)
Electrographic features	
<3 Hz SW	19 (100)
PFA	19 (100)
Focal discharges	12 (63.5)
Frequency of seizures – 3 months before lacosamide	
Tonic seizures/month	
>30	9 (47.7)
20–30	4 (21.1)
10–20	2 (10.1)
<10	4 (21.1)
Astatic seizures/month	
10–20	4 (21.1)
<10	14 (73.8)
Tonic-clonic seizures/month	
<10	15 (78.9)
Focal motor seizures/month	
<5	3 (15.8)
Number of AEDs when LAC was initiated, *n* (%)	
1	4 (21.1)
2	9 (47.4)
3	6 (35.6)
4	0 (0)
Concomitant AEDs, *n* (%)	
VPA	9 (47.4)
TPM	8 (42.1)
LEV	14 (73.7)
CLB	4 (21.1)
VGB	2 (10.5)
LTG	3 (15.8)
Previous callosotomy	4 (21.1)
Previous VNS	7 (36.8)
Previous VNS/Callosotomy	4 (21.1)
Lacosamide	
Initial dose (range)	25 (25–50)
Maximum dose (range)	200 (50–300)
Number of days with lacosamide (range)	90 (25–540)

M: male; F: female; AED: antiepileptic drug; VPA: valproic acid; TPM: topiramate; LEV: levetiracetam; CLB: clobazam; OXC: oxcarbazepine; PHT: phenytoin; VGB: vigabatrin; LAC: lacosamide; PFA: paroxysmal fast activity; LTG: lamotrigine; TCS: tonic-clonic seizures.

patients in which lacosamide was suspended for cluster status or tonic seizures. Nevertheless, the response rate for all seizure types was associated with the etiology ($p < 0.05$).

The median dose required for clinical response was 100 mg for focal (range: 100–250 mg) and tonic-clonic (range: 100–250 mg) seizures. Tonic and astatic seizures worsened with doses of 75 mg (50–100 mg) and did not improve with median doses of 200 mg (Table 3).

Table 2
Efficacy of Lacosamide in children with symptomatic or cryptogenic Lennox–Gastaut syndrome (variation in countable seizures).

Responding rate	Number of patients $N = 19$	Number of patients with symptomatic LGS $N = 7$	Number of patients with cryptogenic LGS $N = 12$
Patients? responding rate Symptomatic $N = 7$ Cryptogenic $N = 12$¶			
100%	0 (0)	0 (0)	0 (0)
>50% < 100	2 (10.5)	2 (10.5)	0 (0)
<50%	1 (5.3)	1 (5.3)	0 (0)
Tonic seizures $N = 19$ Symptomatic $N = 7$ Cryptogenic $N = 12$±			
100%	0 (0)	0 (0)	0 (0)
>50% < 100	1 (5.3)	1 (14.3)	0 (0)
<50%	0 (0)	0 (0)	0 (0)
Unchanged	3 (15.8)	1 (14.3)	2 (16.7)
Increased	16 (78.9)	5 (71.4)	10 (83.3)
Percentage in seizure variation Astatic seizures $N = 18$ Symptomatic $N = 6$ Cryptogenic $N = 12$±			
100%	0 (0)	0 (0)	0 (0)
>50% < 100%	0 (0)	0 (0)	0 (0)
<50%	0 (0)	0 (0)	0 (0)
Unchanged	12 (66.6)	4 (66.6)	8 (66.7)
Increased	7 (38.8)	2 (33.4)	4 (33.3)
Percentage in seizure variation Tonic-clonic seizures $N = 15$ Symptomatic $N = 7$ Cryptogenic $N = 8$±			
100%	0 (0)	0 (0)	0 (0)
>50% < 100	11 (73.3)	5 (71.4)	6 (75)
<50%	2 (13.3)	2 (28.6)	0 (0)
Unchanged	2 (13.3)	0 (0)	2 (25)
Increased	0 (0)	0 (0)	0 (0)
Focal seizures $N = 3$			
100%	3 (100)	3 (100)	0 (0)
Symptomatic $N = 4$ Cryptogenic $N = 5$±			
$N = 9$ (47.3%)†/€	7 (36.8)/2 (10.5)	3 (42.9)/1 (14.3)	3 (25)/2 (16.7)
Symptomatic $N = 4$ Cryptogenic $N = 5$±¥			
$N = 9$ (47.3%)	9 (100)	3(75)/1(25)	3 (60)/2 (40)
Symptomatic $N = 4$ Cryptogenic $N = 5$±≠			
$N = 9$ (47.3%)	9 (100)	3(75)/1(25)	3 (60)/2 (40)

% are referred to the total of the columns. ±mean $p > 0.05$, mean $p = 0.01$.
†/€ Number (%) of patients with tonic status/or repetitive cluster of tonic seizures after introduction of lacosamide.
¥ Number (%) of patients who discontinued LAC due to status or cluster of tonic seizures.
≠ Number (%) of patients that returned to basal seizure rate after lacosamide discontinuation.

3.1. Safety

LAC treatment was associated with worsening of behavioral problems (Table 4). After introduction of LAC, nine out 19 patients (47.3%) presented worsening in the behavior scales. The median in Likert scale before and after LAC introduction remained stable, nevertheless, the lower and upper quartiles increased from 0 to 2 (lower quartile) and from 3 to 4 (upper quartile). This effect reach statistical significance (Wilcoxon Matched pair test $p = 0.007$).

Nine patients (47.7%) reported adverse side effects during treatment with LAC. The most commonly reported adverse events were worsening of seizures, aggressiveness, and irritability, each one in nine patients (47.7%). Somnolence was the second most common reported side effect (31.6%). LAC discontinuation led to reduction to baseline seizure frequency in all of them. There were no significant laboratory anomalies in liver, renal or hematologic functions (Table 5).

It was interesting to find that all patients for whom seizures improved by more than 25% were male, with symptomatic LGS with focal discharges and lesional MRI findings. All of them were on polytherapy regimen with clobazam (Table 6).

Table 3
Lacosamide dose according to responding, worsening or unchanged seizure rate.

Lacosamide doses mg	Median	Minimum	Maximum
Tonic seizures $N=19$			
Responding	200	200	200
Worsening	75	50	100
Unchanged	200	200	250
Astatic seizures $N=18$			
Worsening	75	50	100
Unchanged	200	150	300
Tonic-clonic seizures $N=15$			
Responding	100	100	250
Unchanged	150	100	300
Focal seizures $N=3$			
Responding	100	150	250
Patients with tonic status or repetitive cluster of tonic seizures after introduction of Lacosamide	75	50	100

Table 4
Behavior analysis before and after introduction of Lacosamide.

Behavior analysis (Likert scale)	Score variation on Likert scales after Lacosamide introduction: patients (%)[†††]
0 variation	10 (52.6)
Total of patients with worsening on the behavior scale	9 (47.4)
Increased 1 point	6 (31.6)
Increased 2 points	1 (5.3)
Increased 3 points	2 (10.5)

[†††] Median (range) [lower quartile; upper quartile] Wilcoxon matched pair test, p value [before/after lacosamide]: 2 (0–4) [0;3]/2 (0–4) [2;4]; $p=0.007$.

Table 5
Side effects reported after introduction of Lacosamide.

Side effects $N=9$	Number (%)
Somnolence	6 (31.6)
Aggressiveness	9 (47.7)
Irritability	9 (47.7)
Dizziness	2 (10.5)
Vomiting	3 (15.8)
Euphoria	2 (10.5)
Increased number of seizures	9 (47.7)
Number of patients in whom improvement was noted after reduction of dose	6 (31.6)
Discontinuation of Lacosamide due to side effects other than seizure aggravation	(0)
Lacosamide discontinuation led to reduction of baseline seizure frequency $N=9$	9 (100)
Laboratory anomalies	0 (0)

4. Discussion

LAC has a novel mechanism of action that seems to be different from the existing AEDs in that it selectively enhances the slow inactivation of voltage-gated sodium channels. Also, LAC reduces the ability of (epileptic) neurons to sustain prolonged firing bursts by regulating the long-term availability of voltage-gated sodium channels. In addition, experimental data suggests a synergic effect when used in combination with other AEDs. The aforementioned data led us to expect a beneficial effect of LAC as an add-on treatment.

Thus, LAC has been approved by the licensing authorities in the United States and in the European Union as an add-on treatment of partial seizures in patients with 16 years of age or older. Anecdotal reports on the efficacy of LAC in LGS have been published [10,13,14].

The present study is to our knowledge the first study that describes the follow-up of adult patients with Lennox Gastaut Syndrome treated with Lacosamide.

In an extended review on *pubmed* and *medline* only a few reports of LAC treatment in LGS were found. The results reported are contradictory. Cuzzola et al. [13] reported a paradoxical reaction to LAC in three adult patients with LGS. All of them showed an increased frequency of tonic seizures with tonic status occurring in one of them. All patients returned to their previous clinical condition after drug withdrawal. Andrade-Machado et al. [14] reported a 20-year-old male affected by LGS who showed a clinical exacerbation of tonic seizures after starting LAC. By contrast, Rastogi and Ng [15] showed that LAC was effective in two patients with LGS with more than 90% seizure reduction. Moreover, Casas-Fernández et al. [16] recently described another two patients with LGS who were responsive in terms of seizure control to add-on LAC therapy.

Grosso et al. reported the follow-up of 18 children with LGS. They found a responsive rate of about 30% [10]. The paper published by Grosso et al. received many criticisms. The authors considered the diagnosis of Lennox–Gastaut syndrome in patients without tonic seizures, (4 of 18 (22.2%) of patients). In these cases the diagnosis was based on the accepted ILAE criteria for the classification of seizures and epileptic seizures published in 1989 [17]. Nevertheless, it is well known that tonic seizures should be a prerequisite for the diagnosis of LGS [1]. In that scenario, it is possible that 22.2% of patients reported in this study suffered from multifocal or focal epilepsy. This could be one reason for higher responding rate reported in the aforementioned study, due to the efficacy previously documented for LAC in these epileptic syndromes [18]. It is concordant with our results that showed a 100% of responding rate for focal seizures in patients with focal epileptiform discharges and a lesional MRI. Maybe these patients have been suffering from LGS with focal epilepsy, due to the finding of focal discharges, focal lesion on MRI and the presence of focal seizures. Perhaps many patients with LGS with focal finding in MRI and focal seizures could benefit from an add-on regimen of LAC.

The sub-analysis done with the responding patients who showed focal EEG findings, led us to recommend further studies focused in the possible positive pharmacodynamic interaction between LAC and clobazam. These features have not been reported previously and it should be evaluated in future prospective studies.

On the other hand, as was reported by Andrade-Machado et al. [14], the aggravation of LGS is not only due to the effect of LAC on clinical seizures, but also, because of the worsening of the encephalopathic electrographic patterns (fast rhythms). It is also known that most of the tonic seizures in LGS are subtle and only

Table 6
Analysis of patients with a responding rate by more than 25%.

Cases	Age	Sex	Etiology	Focal seizures	PFA/3 Hz SW	Focal ED	MRI findings	Other treatment	Concomitants AEDS
1	18	M	S	Yes	Yes	Yes	Posterior quadrant gliosis	VNS	LEV + CLB
2	23	M	S	Yes	Yes	Yes	FCD	Callosotomy	LEV – CLB
3	25	M	S	Yes	Yes	Yes	Frontal gliosis	VNS and callosotomy	VPA + VGB + CLB

S, means symptomatic; M, male; SW generalized spikes and waves; ED epileptiform discharges; PFA: paroxysmal fast activity; FCD focal cortical dysplasia.

seen in polygraphic video-EEG recordings [1]. In the study of Grosso et al. [10], the seizure type and frequency were registered by parents and/or nursing staff and reviewed at each follow-up visit. They never mentioned the use of video-EEG recording as a tool for determining a potential electrographic aggravation caused by LAC. Therefore, most of subtle tonic seizures and the rate of fast rhythms before and after treatment could not be recognized. That is why, in our opinion, the efficacy and effectiveness of LAC was not correctly evaluated. The most important aspect is that subtle tonic seizures and fast rhythms have been associated with a cognitive decline in patients with an epileptic encephalopathy [1]. According to this, we did not evaluate our patients with polygraphic studies during the follow-up, but the worsening of behavior documented in the present study could be explained at least by worsening in the encephalopathy associated with this epileptic syndrome secondary to the use of LAC [14]. The aggravation of seizures and behavior cannot be explained by drug-to-drug interaction because the administration of LAC to extensive or poor metabolizers of the cytochrome P 450 subsystem 2C19 has showed that there is no relevant effect on metabolism and elimination of LAC by this system. In addition, a recent pharmacokinetic study excluded an interaction of clinical significance between LAC and other AEDs [19,20]. Therefore, we can exclude LAC-induced aggravation of LGS due to pharmacokinetic interactions with other AEDs.

The incidence of side effects reported with LAC treatment varied from 29% to 61%. Our range of side effects is similar to those reported previously in the literature [4,21,22]. Most adverse effects seen with LAC in adults are dose-related and are reversible upon discontinuation or dose reduction. In adults, LAC doses up to 400 mg/day may be well tolerated [4]. The range dose of LAC in our study was (50–300)/day, with an incidence of adverse events of 47.4% [21,22].

Dosage reduction was necessary in all patients with worsening seizures and in all of them it was followed by a seizure frequency reduction to the baseline rate. The percentage of patients with increased seizure frequency (47.4%) found in the present study is greater than what was the reported by Grosso et al. study, but is congruent with the previously reported effects in this epileptic syndrome by us and Cuzzola et al. [13,14]. A diagnosis of paradoxical reaction can be made in these patients due to the fact that all of them returned to baseline seizure rate after LAC discontinuation.

Despite of possible worsening of behavior, tonic and astatic seizure frequency, it is interesting the combination of suppression of generalized tonic-clonic and focal seizures, induced by LAC, found in the present study.

The electroclinical features of an epileptic syndrome can be considered as reflecting the specific cerebral networks being recruited. In this context, a neural network comprises anatomically and functionally connected cortical and subcortical brain structures, where activity in any one part of the network, may affect activity in all the others. Simultaneous measurement of EEG and fMRI has demonstrated two different patterns of cortico-subcortical activation in patients with LGS [23,24]. GPFA, the electrographic pattern associated with tonic seizures, has been associated with activation across broad areas of cortex, but appears to spare the primary cortices. GPFA shows increased BOLD signal in a number of subcortical structures including the thalamus, basal ganglia, and brainstem, all known to have broad connections to the "association cortices". This observation of activation in many areas associated with association cortex and its subcortical system, but excluding primary cortex, has led investigators to call the network activation "diffuse association network activation" (DANA). A different scenario is seeing in some patients with LGS, even though the EEG appeared to be generalized, the BOLD signal characteristics of discharges had lateralized features or even suggestions of focality. In these cases, the above-mentioned findings were concordant with the EEG or structural findings. This suggests that cortical lesions can be activated along with this diffuse activation of the association networks (DANA), possibly co-opting it as an epileptic network or at least engaging this system in the epileptic activity in LGS. Thus, focal ictal onset zone can activate secondarily this DANA, resulting in the same electroclinical phenotype (LGS). EEG-fMRI maps may be showing both the DANA and an epileptogenic focus that is likely to drive the network instability. These notions have been also supportive by SPECT and PET studies [24].

We should analyze our results in face of this "secondary network disorder". The improvement in seizure rate and focal seizures in our cohort can be explained by these hypotheses, because LAC is very effective in control of partial onset seizures, according to double blind placebo-controlled clinical trials [6–9]. Thus, in this subgroup of patients, LAC could inhibit an epileptogenic focus and therefore, prevent seizures arise from it.

Our study have some weaknesses that make difficult to extrapolate it to other scenarios, these include: first, the retrospective nature and the small series of patients. However, the study design reflects daily clinical practice and provides a more realistic view of the use of LAC in adults. The size of our population was not so large to able us to draw more definite conclusions and therefore, we recommend further clinical trials to validate or to refuse our data. The study was carried out in a tertiary center that did not necessarily reflect all scenarios, but as we are treating a severe epileptic syndrome, almost all patients with LGS are actually treated in a highly specialized center for treatment of these epileptic syndromes. However, caution is still necessary when the drug is used in adults with LGS, because our preliminary observations suggest that LAC might exacerbate tonic and astatic seizures and also the encephalopathy associated with this epileptic syndrome. Thus, we do not recommend the use of lacosamide in adults with LGS.

5. Conclusions

Lacosamide may not be effective to treat patients with adult Lennox Gastaut syndrome as it can exacerbate tonic and astatic seizures, and the encephalopathy associated with this epileptic syndrome. It is interesting to consider the likelihood of suppression of generalized tonic-clonic and focal seizures, due to the fact that these seizures might be the most disabling seizure types in some adults with LGS. That is why; LAC could be an option after carefully balancing risks and benefits in each individual case.

Journal position on ethical publication

We have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of interest

The authors have not received any support and/or have not served as paid consultants for the study. None of the authors has any conflict of interest to disclose.

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